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Your ref	Our ref	Direct Line	Date
	SYN 60012/WO	+44 1642 52 2650	28th January 2005

Dear Sirs,

International Patent Application Number : PCT/GB2004/001639
Johnson Matthey PLC
Response to Written Opinion dated 08.12.2004

1. Correction under Rule 91 PCT

The Applicant hereby requests a correction of a typographical error under Rule 91 PCT. We request that the word "morpholine" at page 7, line 13 of the description be replaced with the word "ephedrine". We submit that the correction is obvious and that the skilled person would recognize that nothing else was intended. The reasons are as follows;

a) that 'morpholine' is the wrong word.

We submit that the skilled person would immediately realize that (+)-N-methyl-*morpholine* was incorrect because;

i) It is not mentioned anywhere else in the specification.
ii) It is not an alkanolamine as required in the application as originally filed.
iii) It is not chiral and so the prefix (+) immediately indicates an error to the reader.
iv) The Example gives a product with an ee of 67%, which is impossible without a chiral molecule being present.
v) The weight used in Example 2 (5.7g) does not correspond to 32 mmol of N-methyl-morpholine. 5.7 g corresponds to 56 mmol N-methyl-morpholine.

b) that 'ephedrine' is the correct word.

We submit that the skilled person would immediately realize that N-methyl-*ephedrine* was the correct word because;

i) N-methylephedrine is indicated as the most preferred alkanolamine at page 3, lines 12-15.
ii) It is an alkanolamine as required in the application as originally filed.
iii) There are no other 'N-methyl' alkanolamines mentioned anywhere in the specification.
iv) Both examples relate to the synthesis of (R)-2-methylhex-3-yne-2,5-diol and the comparative example uses (+)-N-methylephedrine.

v) The weight used in Example 2 (5.7g) corresponds exactly to 32 mmol of N-methyl-ephedrine.

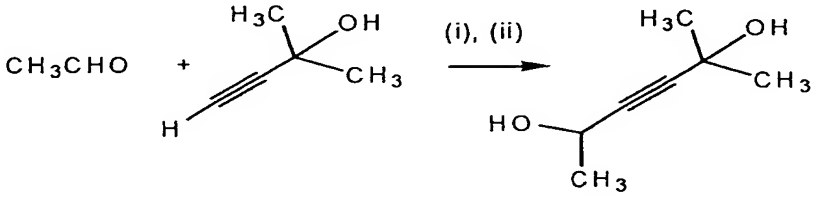
For these reasons we request the correction and accordingly that Examiner consider the Example 2 as relating to the claimed invention.

Please find enclosed a replacement page 7 incorporating the requested correction to line 13.

2. Inventive Step

The Examiner has identified D1 and D3 as closest prior art. The difference between D1 and D3 and the present invention as claimed in claim 1 is in the process used to synthesis hydroxyalkynes using acetaldehyde. The problem to be solved therefore is to provide a process for performing coupling reactions between acetaldehyde and a terminal alkyne. Neither D1 nor D3 mention acetaldehyde, and comparative Example 1 clearly shows that the general methods for coupling reactions as described in these earlier publications are unsuited to using acetaldehyde as the yields of hydroxyalkyne are always <20%. Example 2, as corrected, shows the problem is solved by the present invention as claimed. We therefore submit that claim 1 has an inventive step over D1 and D3.

We also submit, if the correction requested under Rule 91 is rejected, a further example, in which N-methylephedrine is used.



(I) (II)

Step (i): Zinc triflate (10.9 g, 30 mmol, 1.5 eq), (+)-*N*-methylephedrine (5.7 g, 32 mmol, 1.6 eq), DBU (4.8 mL, 32 mmol, 1.6 eq) and 2-hydroxy-2-methyl-3-butyne (Alkyne 1, 80 mL) were stirred at room temperature for 2 h. Step (ii): a solution of acetaldehyde (1.13 mL, 20 mmol) in toluene (50 mL) was then slowly added over a 4 hour period. After stirring overnight at room temperature, the reaction was quenched by addition of sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with methyl-tertiary-butyl ether (MTBE) (2 x 50 mL). The combined organic layers were washed with sat. aq. NaCl (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the crude material by filtration through a plug of silica afforded 2.25 g of (II) as a yellow oil in 87% yield and 67% ee as determined by GC analysis. GC method: Lipodex-E column, 95 °C, 55 psi, retention time: 16.6 min (minor isomer), 17.5 min (major isomer).

The above experiment was repeated whereby the second step (ii) was carried out at 0°C or -10°C. The yields were 50% or greater and the enantioselectivities were also 67%.

This example demonstrates the surprising effect that by omitting the solvent for metal-alkyne complex formation the process of the present invention provides acetaldehyde-derived hydroxyalkynes in high yield.

3) Article 6 PCT

a) Thermal fragmentation. We submit that the information relating to thermal fragmentation does not render the claims 1-5 unclear as the information merely relates to a possible use for the hydroxyalkyne product obtained from the process of claims.

b) "substantially". We desire to delay amendment of the description in respect of the word "substantially" appearing on page 4 line 2 until the national phase in view of the different requirements of the designated national and regional offices.

4) Rule 5.1 (a)(ii) PCT

Mention of D4 and D5. We desire to delay amendment of the description to include these prior art references until the national phase in view of the different requirements of the designated national and regional offices.

Yours Faithfully

Sara H, M. Gibson
Authorised Representative
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Example	Solvent	$Zn(OTf)_2$ eq[2]	Base	Base eq[2]	Alkanol-amine ligand	Ligand eq[2]	Temp.	Yield %	ee[4] %
1.1	Toluene	1.1	Et_3N	1.2	nme[3]	1.2	23	<20	60
1.2	Toluene	1.1	Et_3N	1.2	nme	1.2	30	0	-
1.3	Toluene	1.1	Et_3N	1.2	nme	1.2	40	0	-
1.4	CH_2Cl_2	1.1	Et_3N	1.2	nme	1.2	20	0	-
1.5	Toluene	1.1	iPr_2EtN	1.2	nme	1.2	20	<20	50
1.6	Toluene	1.1	pyridine	1.2	nme	1.2	20	0	-
1.7	Toluene	1.1	DBU	1.2	nme	1.2	20	<20	60
1.8	Toluene[1]	1.1	DBU	1.2	nme	1.2	20	0	-
1.9	iPrOH	1.5	DBU	1.6	nme	1.6	20	0	-

1. Solvent increased by a factor of 20 (volume).
2. eq = equivalents, i.e. moles per mole acetaldehyde
3. nme = (+)-N-methylephedrine.
4. ee% = enantiomeric excess

In all cases the yield of (R)-2-methylhex-3-yne-2,5-diol (II) was always less than 20% (based on acetaldehyde). Changing the solvent, base and relative amounts of zinc triflate, base and alkanolamine ligand did not increase the yield.

Example 2: Reaction of acetaldehyde with 2-methyl-3-butyn-2-ol

Step (i): Zinc triflate (10.9 g, 30 mmol, 1.5 eq), (+)-*N*-methylephedrine (5.7 g, 32 mmol, 1.6 eq), DBU (4.8 mL, 32 mmol, 1.6 eq) and 2-hydroxy-2-methyl-3-butyne (Alkyne 1, 80 mL) were stirred at room temperature for 2 h. Step (ii): a solution of acetaldehyde (1.13 mL, 20 mmol) in toluene (50 mL) was then slowly added over a 4 hour period. After stirring overnight at room temperature, the reaction was quenched by addition of sat. aq. NH_4Cl (50 mL). The aqueous layer was extracted with methyl-tert.iary-butyl ether (MTBE) (2 x 50 mL). The combined organic layers were washed with sat. aq. NaCl (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the crude material by filtration through a plug of silica afforded 2.25 g of (II) as a yellow oil in 87% yield and 67% ee as determined by GC analysis. GC method: Lipodex-E column, 95 °C, 55 psi, retention time: 16.6 min (minor isomer), 17.5 min (major isomer).